REMARKS

Applicants appreciate the Examiner's time and consideration given the application and the discussion thereon. Favorable reconsideration is requested in view of the foregoing amendments and the following remarks.

I. Claim Status and Amendments

Claims 1, 3, 5, 7, 8, 54, and 55 were pending in this application when last examined and stand finally rejected. Claims 2, 4, 6, and 9-53 were previously cancelled. No claims have been allowed.

Claims 1, 54, and 55 have been amended by way of this response. See the discussion below for the support for the amended claim language.

Briefly, claim 1 relates to a method for preferentially generating oligodendrocytes of the $O1^+$ and/or $O4^+$ phenotypes by growing neurosphere (NS) cells in a culture medium that promotes preferential differentiation of such NS cells into such oligodendrocytes. The culture medium comprises one or more gp130 activators selected from the group consisting of CNTF, OSM, IL-6, IL6R/IL6 chimera and IL-11.

By way of the present amendment, claim 1 has been amended to clarify that, with the presence of the specific culture medium of the claims, the method results in

specifically enhanced differentiation (*i.e.*, preferential differentiation) along the oligodendrocyte lineage into $O1^+$ and/or $O4^+$ oligodendrocytes. It is believed that the specification provides explicit and/or implicit support for the amended claim language. For instance, the title of the case is "Enhancement of Oligodendrocyte Differentiation." Also, further support can be found in the specification, for example, at page 6, lines 12-15, at page 9, lines 1-3, at page 10, lines 5-8 and lines 15-20, and the Examples (e.g., Example 4 on pages 33-34, Example 5 on pages 35-36, in particular, lines 9-13 on page 36, Example 6 on pages 36-37, and Example 7 on pages 37-38). The examples show that the differentiation in accordance with the present invention is preferential toward oligodendrocytes, as opposed to the other lineages of neuronal progenitor cells. See, for instance, the disclosure, at page 10, lines 19-20, which states: "Hence, IL6R/IL6 chimera showed a specific effect on promoting the differentiation of the neurosphere cells toward the oligodendrocyte lineage."

Thus, the specification fully supports that the claimed method is a method to specifically enhance differentiation of ES cells into the $O1^+$ and or $O4^+$ oligodendrocyte lineage, thereby causing the NS cells to differentiate along the oligodendrocyte lineage into $O1^+$ and/or $O4^+$ oligodendrocytes. No new matter has been added.

Support for new claim 56 can be found at page 37, lines 25-32 (Example 7). Support for new claim 57 can be found at page 36, lines 30-33 (Example 6). No new matter has been added.

Claims 1, 3, 5, 7, 8, and 54-57 are pending upon entry of this amendment, and these claims define patentable subject matter warranting their allowance for the reasons discussed herein.

II. Prior Art Rejections

Claims 1, 3, 5, 7, 8, and 54-55 were finally rejected under 35 U.S.C. 102(b) as being anticipated by Carpenter (WO01/88104) as evidenced by Bauman for the reasons set forth in item 6 on pages 3-6.

In particular, the Examiner states that Carpenter teaches a method of differentiating oligodendrocytes comprising growing primate pluripotent stem cells, including human embryonic stem cells, in the presence of a gp130 activator. The Examiner again contends that Carpenter teaches neurosphere cells derived from ES cells at page 19, lines 10-35. The Examiner acknowledges that Carpenter does not explicitly teach expression of $O4^+$ and $O1^+$ markers on differentiated oligodendrocytes, but that the expression of these markers is an inherent feature of differentiated

oligodendrocytes, as evidenced by Baumann. This rejection is respectfully traversed.

As best as can be understood by Applicants, the Examiner has maintained this rejection on the basis that as long as the prior art culture medium includes a gp130 activator and discloses a method resulting in precursor cells differentiating "into a cell mixture encompassing different neural cells including neural progenitor cells, mature oligodendrocytes, astrocytes and neuronal cells" including $O1^+$ and/or $O4^+$ oligodendrocytes, and starting with cells that are derived from ES cells, the claim is anticipated. The Examiner further states that the claimed method fails to limit the percentage of $O1^+$ and/or $O4^+$ oligodendrocytes and the specification fails to show that only pure homogeneous $O1^+$ and/or $O4^+$ oligodendrocytes are produced.

In reply, Applicants have amended the claims in manner believed to overcome this concern and to obviate the rejections. As discussed above, the present claims have been amended to specify that they are specifically enhancing differentiation into the $O1^+$ and or $O4^+$ oligodendrocyte lineage, thereby causing the NS cells to differentiate along the oligodendrocyte lineage into $O1^+$ and/or $O4^+$ oligodendrocytes. As such, the claimed method predominantly results in preferential differentiation into $O1^+$ and/or $O4^+$

oligodendrocytes. It does not result in production of the "mixture of cells" as disclosed in Carpenter and as acknowledged by the Examiner. See the Examples in the disclosure, which show that the differentiation in accordance with the present invention is preferential toward oligodendrocytes, as opposed to the other lineages of neuronal progenitor cells.

Indeed, the amended language in claim 1 requiring this preferential differentiation seemingly excludes the prior art teaching of Carpenter resulting in the mixture of cells.

In fact, nowhere does Carpenter disclose the use of a culture medium in a method to specifically enhance differentiation to cause the NS cells to differentiate along the oligodendrocyte lineage into $O1^+$ and/or $O4^+$ oligodendrocytes. Instead, as argued in the last response, Carpenter relates to differentiation into a mixture of neuronal cells in general. Also, as noted in the last response, there is no example in Carpenter of specific differentiation into oligodendrocytes. In Example 3, a cocktail of differentiation factors was used to cause A2B5-positive cells to mature into neural cells that include oligodendrocytes, astrocytes and also a large proportion of neurons. Note that only about 13% of the mature cells were

GalC positive, indicating that they may be oligodendrocytes. CNTF was only one of six factors that were used.

Also, Applicants again submit that Carpenter does not start with neurospheres. There is no disclosure that the neural precursor cells of Carpenter are the neurospheres discussed in the present specification and described as "neurotube-like rosettes" in the Zhang et al. (2001) publication discussed in the specification (a copy of which was previously submitted). See reference thereto in the present specification, for example, at page 10, lines 9-10. An embryoid body is not a neurosphere and *vice versa*.

Accordingly, as Carpenter does not begin with neurospheres and the culture medium of Carpenter does not promote the preferential differentiation of NS cells into a oligodendrocyte lineage as recited in the claims, none of the present claims are anticipated by Carpenter.

Furthermore, new claims 56 and 57 specify that "said culture medium promotes myelinating activity" and "said culture medium resulted in formation of large and highly branched $O1^+$ and/or $O4^+$ oligodendrocytes exhibiting large myelin membranes", respectively. Support can be found in the disclosure at page 36, lines 30-33 (Example 6) and at page 37, lines 29-32 (Example 7). Carpenter does not disclose these newly claimed features.

For these reasons, it is clear that Carpenter fails to disclose each and every element of the claims, as required for anticipation. Therefore, Carpenter cannot anticipate the claims.

Accordingly, reconsideration and withdrawal of this rejection are respectfully urged.

In item 7 on page7, claims 1, 3, 5, 7, 8, and 54-55 were finally rejected under 35 U.S.C. 102(b), as being anticipated Gearhart, as evidenced by Baumann.

The Examiner argues that Gearhart teaches a method of differentiating oligodendrocytes by growing ES cells in the presence of a gp130 activator. The Examiner states that this patent also teaches neurosphere cells and the production of oligodendrocytes with $O4^+$ and $O1^+$ markers. This rejection is respectfully traversed for essentially the same reasons set forth above in the traversal to the first prior art rejection.

As discussed above, the present claims have been amended to specify that they are specifically enhancing differentiation into the $O1^+$ and or $O4^+$ oligodendrocyte lineage, thereby causing the NS cells to differentiate along the oligodendrocyte lineage into $O1^+$ and/or $O4^+$ oligodendrocytes. Gearhart does not disclose or suggest this. Gearhart fails to disclose a culture medium that promotes the preferential

differentiation into oligodendrocytes as claimed. Gearhart only teaches generalized differentiation and does not teach how to obtain preferential differentiation into oligodendrocytes.

Also, Gearhart nowhere teaches neurosphere cells. A neurosphere cell is distinctly different from an embryoid body, as disclosed in Gearhart. In this regard, the instant application discloses that the NS cells are derived from embryoid bodies and the Zhang et al (2001) reference referred to in the specification specifically teaches how to obtain NS cells from embryoid bodies. The Examiner's reference to a discussion of embryoid bodies says nothing about differentiation of neurospheres as claimed.

For these reasons, Gearhart cannot anticipate the claims presently amended. Thus, reconsideration and withdrawal of this rejection are also respectfully urged.

III. <u>Indefiniteness Rejections</u>

Claims 54 and 55 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite, for the reasons in item 8 on pages 8-9 of the Office Action.

Applicants have amended the claims in a manner believed to overcome this rejection. Specifically, claims 54

and 55 are amended to better conform to US practice for antecedent basis.

As to the Examiner's other concern with respect to claim 54, Applicants believe that the language of the claim clearly requires that the one or more gp130 activators is the only growth or differentiation agent present in the culture medium. In effect, this language clearly specifies that the culture medium does not have other growth factors in it. Applicants fail to see how this is indefinite or somehow inconsistent. This claim language is also clearly define in the specification, for example, in the last paragraph on page 14, where it states that the gp130 activator is added to the NS cells to promote formation of oligodendrocyte progenitors "either alone or together with other growth or differentiation agents such as retinoic acid, EGF, PDGF etc." (Emphasis added).

Thus, it is believed that this language is clear on its face. It is not ambiguous, nor is it indefinite.

The claims are thus clear, definite and have full antecedent basis. This rejection is believed to be overcome, and withdrawal thereof is respectfully requested.

VI. Conclusion

Having addressed all the outstanding issues, this paper is believed to be fully responsive to the Office Action. It is respectfully submitted that the claims are in condition for allowance and favorable action thereon is requested.

In the event that the Examiner disagrees and maintains one or more of the rejections, then kindly contact the undersigned attorney at the telephone number below to discuss comments or proposals for expediting prosecution.

Respectfully submitted,

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